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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/424,521	02/15/2000	PETER E. NIELSEN	ISIS-3070	8096

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EXAMINER

SCHULTZ, JAMES

ART UNIT

PAPER NUMBER

1635

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/424,521

Applicant(s)

NIELSEN, PETER E.

Examiner

J. Douglas Schultz

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-- The MAILING DATE of this communication appears on the cover sheet with the corresponding address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21,23-27,31-34,38-41,45-48 and 52 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 21,23-27,31-34,38-41,45-48 and 52 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). ____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ 6) ☐ Other: ____

DETAILED ACTION

Response to Arguments

Applicants' response filed July 3, 2002 has been considered. Rejections and/or objections not reiterated from the previous office action mailed April 3, 2002 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Claims 23, 25-27 and 31 are rejected under 35 U.S.C. 102(a) as being anticipated by PCT Patent Application WO/92/20702 for reasons of record. Applicants' arguments filed July 3, 2002 have been fully considered but they are not persuasive. Applicants argue that the rejection of claims 23, 25-27 and 31 made in the previous Office Action under 35 U.S.C. 102(a) over PCT Patent Application WO/92/20702 ("the 702 application") should be withdrawn, because Applicants assert that the 702 application does not actually describe the claimed invention in a way that would place it in the possession of those skilled in the art, and that the examiner therefore must have engaged in picking and choosing from among many variables of pages 8-10 of the 702 application.

This argument is not adopted, since the compounds of the 702 application are substantially identical to the presently claimed compound. Furthermore, the scope of all possible embodiments of structure III of the 702 application (pages 7-10) is substantially the same as the instantly claimed product. Structure III of the 702 application provides a generic structure of a peptide nucleic acid (PNA), which is also the subject of the present application. Structure III is

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identified as the preferred embodiment of such a PNA, shares identical core structure with and possesses all of the limitations of the presently claimed compounds and thus clearly anticipates said compounds. Specifically, both structure III of the 702 application and the instantly claimed compounds possess identically placed carbon/nitrogen structures, along with R_h , L, R_7 and R_i groups (the instantly claimed compositions also comprises an R_j group that may become part of the R_i group). The R_h groups of both the instantly claimed compositions and of the structure III composition may only be OH, NH₂, or NHlysNH₂. The L-groups of both may be naturally occurring nucleobases. The R_7 groups of both may either be a hydrogen or an amino acid. Finally, the language of the instant claims allows for merging R_i and R_j into one group that is analogous to the R_i group of structure III of the 702 application, and both may be alkyl groups. Contrary to Applicants' assertion, there are not many variables from which to choose from; in fact, the scope of variables is quite close between the reference and the instantly claimed composition. Thus, all elements of the presently claimed compounds are present, rendering the instantly claimed compounds and related methods as being clearly anticipated by the teachings of the 702 application.

Regarding Applicants' arguments that the examiner engaged in picking and choosing to produce the claimed compound, as explained above, structure III teaches all the elements of the presently claimed compound. Further, the compounds of the 702 application contain relatively few options for substitution, most of which match identically with the substitutions claimed in the instant application. Thus, there is no extensive "laundry-list" of substituents as implied in Applicants' arguments from which to pick and choose in producing the instantly claimed application (see pages 7-10 of the 702 application). Moreover, Applicant argues that picking and

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choosing is inconsistent with the finding of anticipation, and refers to legal precedent for support. *In re Schaumann* 197 USPQ 5, @7-10 (CCPA 1978). The examiner asserts that the anticipating reference provides very few options for substitutions, and the options that are presented are very similar to the presently claimed scope and thus did not require the picking and choosing that applicant alleges. Finally, it should be noted that applicants recital of *In re Schaumann* used to support applicants arguments is attributed to the lone dissenting opinion of the lower court, which is not affirmed in the cited case. Nevertheless, because all elements of the compound are anticipated in the reference, and because the scope of compound of the 702 application is identical in most respects to the scope of the compound of the instant claims, there was no picking and choosing necessary to produce the instantly claimed product, thus rendering applicant's arguments unpersuasive.

Claims 21, 23-27, 31-34, and 38 rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teaching of the 702 application and Renneissen et al. (J. Biol. Chem, (1990), 265 pp.16337-16342), for reasons of record. Applicants' arguments have been fully considered but they are not persuasive. Applicants argue that there is no motivation to combine the elements of the reference into the compound of the instant application and that therefore the examiner reverted to picking and choosing from among the elements of the reference to produce the invention as claimed. Further, Applicants argue that the elements of the presently claimed invention are not present in the combination of the 702 application and Renneisen et al., and that there is no motivation to combine such references.

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The arguments regarding Applicants' claim that there is no motivation to combine the elements of the 702 application to produce the instantly claimed invention are addressed above. Briefly, since all elements of the instantly claimed compound are anticipated in the reference, and because the scope of compound of the 702 application is identical in most respects to the scope of the compound of the instant claims, there was no picking and choosing necessary to produce the instantly claimed product. Further, since the compound of the present invention is anticipated by the reference as discussed above, the rejection of obviousness as set forth in the previous office action was primarily directed to the *combination* of the instant compound and its use in liposomes.

Applicants argue against such combination on the grounds that Renneisen et al. discuss the use of RNA oligonucleotides encapsulated into liposomes, and does not teach PNAs encapsulated into liposomes. In response to these arguments against Renneisen et al., Applicants are basically saying that Renneisen et al. does not teach the instant invention as a whole. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The previous Office Action was not relying upon Renneisen et al. to teach PNA encapsulation in liposomes, as a whole; rather, Renneisen et al. was relied upon to teach that any oligonucleotide, including modified nucleic acids (see para. 1-3 of introduction) may be so encapsulated. It therefore would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to encapsulate the PNA oligos of the 702 application in the liposomes as taught by Renneisen et al.,

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for the purpose of enhancing oligo delivery and reducing nuclease degradation, as discussed in the previous Office Action.

Claims 39-41, 45-48, and 52 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record.

Applicant's arguments have been fully considered but they are not persuasive. Applicants argue that the specification discloses adequate support, including sites and modes of administration, dose level and administration regimens. Applicants also argue that therapeutic data is not needed to adequately teach that effect, and that some experimentation is allowed to determine optimum parameters of treatment.

These arguments are not adopted. As discussed in previous Office Actions, the present invention is complex, and therapeutic applications using compounds analogous to those claimed here are undeveloped. The reason they are undeveloped is that there remain several well-known but unsolved problems in the art that persist as obstacles to the practice of the invention as claimed. As previously outlined, and despite the prophetic treatment regimens provided in applicant's disclosure, the ability of the oligos to penetrate cells and reach their targets is largely unpredictable. These compounds are poorly taken up by cells. Once inside the cell, the RNA targets typically have already assumed folded conformations that prevent oligo hybridization to the target, further decreasing the likelihood of predicting success. Further, the immune system

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response to foreign matter in general, and oligonucleotides and their derivatives in particular, can be dramatic and irregular, and can lead to a number of maladaptive responses. Finally, oligonucleotides and their derivatives can bind unpredictably to blood proteins and other elements, further complicating efforts to predict *a priori* whether a particular PNA treatment will ever work. Applicants' response is notably silent in addressing these issues that were raised in the previous Office Action., and has provided no evidence to rebut the teachings outlined above.

Since these issues remain unresolved in the art, and since the prophetic guidance disclosed in the specification does not address how to overcome these obstacles, one of ordinary skill in the art would not be able to make and use the invention without undue experimentation with any predictable degree of success.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355.

The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

J. Douglas Schultz, PhD
October 10, 2002



ANDREW WANG
SUPERVISORY PATENT EXAMINER
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